



3방향복합전위에 의한 8q23.1-q24.13 결실을 가진 Langer-Giedion 증후군

Langer-Giedion Syndrome with 8q23.1-q24.13 Deletion by Complex Three-way Translocation

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Langer-Giedion syndrome is a very rare genetic disorder that is caused by the deletion on chromosome 8q24.1, encompassing the *TRPS1* and *EXT1* genes. We describe a 5-month-old female patient who was admitted to our hospital with clinodactyly and weakness in both thumbs. The patient's karyotype was 46,XX,der(4)t(4;19)(q27;q11),der(8)t(4;8)(q27;q22.3),der(19)t(8;19)(q22.3;q11)del(8)(q23q24.1). Multiplex ligation-dependent probe amplification (MLPA) analysis showed that the patient had a heterozygous deletion, *rsa* 8q24(P064)x1 and *rsa* 8q24(P245)x1. Array comparative genomic hybridization (CGH) analysis further revealed three interstitial deletions spanning a total of 13.7 Mb at 8q23.1-q24.13. Based on clinical findings and confirmation by cytogenetic, MLPA, and array CGH analyses, the patient was diagnosed with sporadic Langer-Giedion syndrome with three-way translocations. This is the first case of Langer-Giedion syndrome with complex chromosomal rearrangements in Korea.

Key Words: Langer-Giedion syndrome, Three-way translocation, 8q24.1, *TRPS1*, *EXT1*

INTRODUCTION

Langer-Giedion syndrome (LGS), also called trichorhinophalangeal syndrome type II (TRPS2) (OMIM #150230) is a very uncommon genomic disorder caused by contiguous gene deletion of 8q24.1, which includes the genes, *TRPS1* and *EXT1* [1, 2]. LGS

is characterized by craniofacial dysmorphisms (bulbous nose, prominent philtrum, thickened alae nasi, and large prominent ears), ectodermal anomalies (sparse, slowly growing scalp hair), skeletal abnormalities (short stature, brachydactyly), multiple osteochondromas, and intellectual disability [3, 4]. Here, we present a case of LGS with complex chromosomal rearrangements. This case is the second report worldwide on the complex chromosomal rearrangement causing LGS and the first such report in Korea [3].

CASE REPORT

The patient was a 5-month-old girl, born at 39 weeks of gestation with a 3.8 kg birth weight, and with chief symptoms of clinodactyly and weakness in both thumbs. She had facial dysmorphisms such as brachycephaly, a bulbous nose, prominent alae nasi, thick nasal septum, prominent ears, and a missing uvula. She also had

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prominent big toes. She showed normal head circumference, and low normal growth in weight (25th percentile), and height (25th percentile) at 9 months. X-ray imaging revealed hypoplasia of both the fifth middle phalangeal bones and hyperextension in both thumbs. The patient did not display definite cone-shaped epiphysis or exostosis. Brain MRI indicated a brachycephaly appearance and a dark signal intensity along the right cerebellar tentorium on SWI. In head CT, the patient showed prominent metopic suture and anterior fontanelle. Abdominal ultrasound, electroencephalogram, echocardiography, and chest X-rays revealed no abnormali-

ties. The patient showed normal hearing function as tested by tympanometry and auditory brainstem response. To assess developmental delay, the Denver development screening test was performed at 8 months. She had delayed personal and social development (delayed by 3 months), fine motor adaptive development (delayed by 2 months), language development (delayed by 1 month), and gross motor development (delayed by 2 months). She showed delayed growth in weight (10th percentile), and height (10th percentile), at 19 months.

Cytogenetic analyses were performed according to the standard

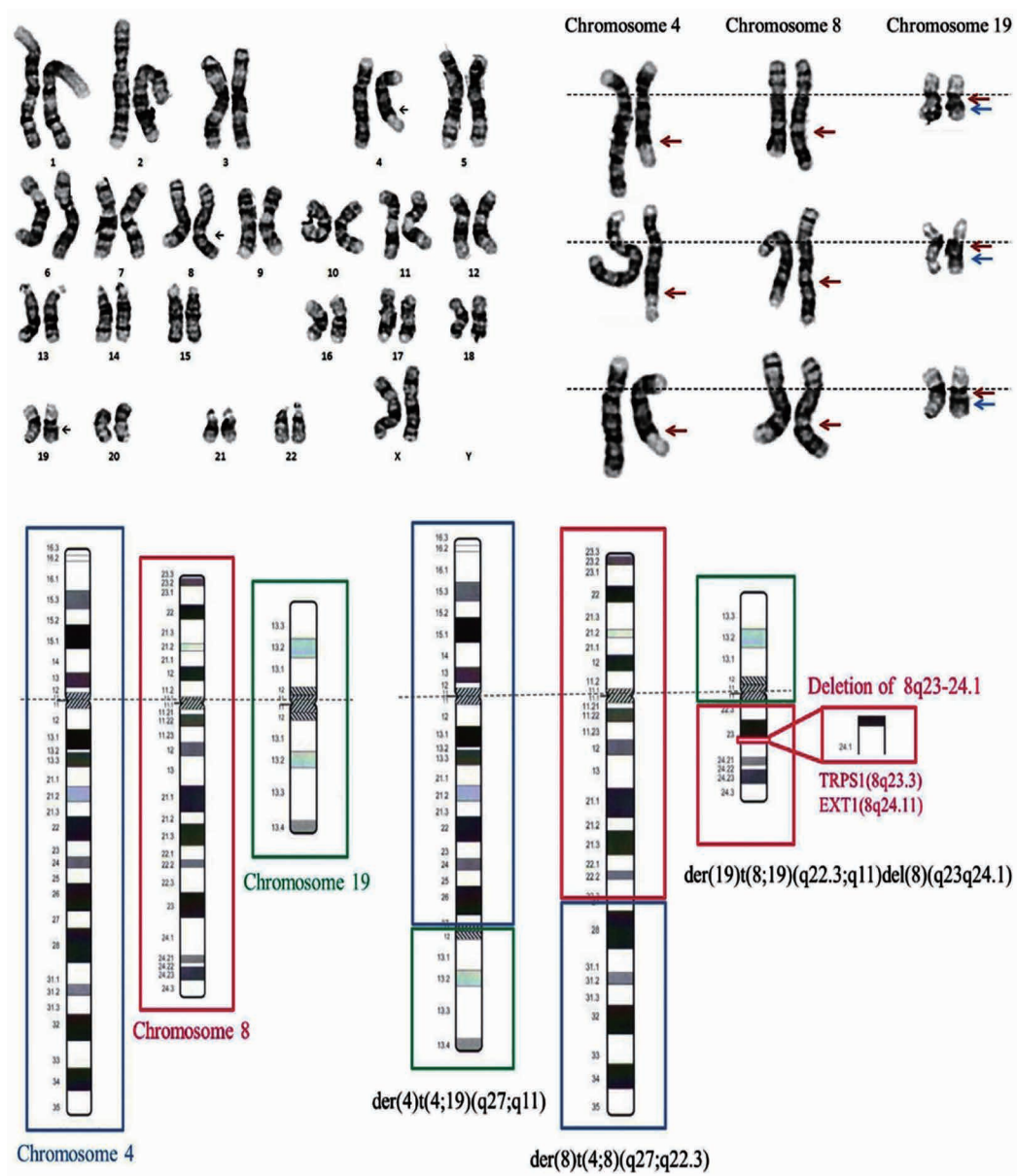


Fig. 1. Cytogenetic analysis of the patient reveals a three-way translocation with an interstitial deletion in 8q23-q24.1.

procedures. The patient's karyotype was 46,XX,der(4)t(4;19)(q27;q11),der(8)t(4;8)(q27;q22.3),der(19)t(8;19)(q22.3;q11)del(8)(q23q24.1) (Fig. 1). She had three-way translocation with interstitial deletion in 8q23–q24.1. The chromosome analysis results of her parents were normal. Therefore, this was a case of *de novo* chromosomal abnormality. Multiplex ligation-dependent probe amplification (MLPA) was performed using MLPA probe mix P064 and P245 (MRC, Holland). The patient had a heterozygous deletion, *rsa* 8q24(P064) x1 and *rsa* 8q24(P245)x1, which was found using probes for *TRPS1* and *EXT1*. The deletion was confirmed and visualized at the molecular level by array comparative genomic hybridization (CGH). The array CGH was carried out using a human whole-genome 180K CGH microarray (Agilent SurePrint G3), which showed three interstitial deletions encompassing *TRPS1* and *EXT1*, suggesting complex rearrangements (Fig. 2). The total size of the interstitial deletion was 13.7 Mb at 8q23.1–q24.13. The deletions at chromosome 8q encompass 45 genes, including the following 10 OMIM genes: *TRHR*, *TRPS1*, *EXT1*, *TNFRSF11B*, *COLEC10*, *TAF2*, *RNF139*, *NDUFB9*, *WASHC5*, and *NSMCE2*.

DISCUSSION

Most cases of LGS are caused by a simple interstitial deletion at 8q23–q24, ranging from 8 to 13 Mb. However, our present case had complex chromosomal rearrangements, with 3-way translocation among 4q27, 19q11, and 8q22.3, and three interstitial deletions on 8q23.1–q24.13, spanning a 13.7 Mb-sized region.

Cappuccio et al. [3] reported a similar case of LGS with complex chromosomal rearrangement. Their case had a 7-Mb deletion at 8q23.3–q24.1 with balanced reciprocal translocation t(2;11)(p24;p15) and showed a feature of Cornelia de Lange syndrome-4 (CdLS-4) due to the deletion of *RAD21* on 8q24 between *TRPS1* and *EXT1*. Recently, many LGS cases have presented with LGS features combined with CdLS-4, which is characterized by distinctive craniofacial features such as synophrys, highly arched eyebrows, long eyelashes, a short nose with anteverted nares, small widely spaced teeth, and microcephaly [3, 5]. However, the patient in this study had two copies of *RAD21* through complex rearrangement and did not show the features of CdLS-4 (Table 1).

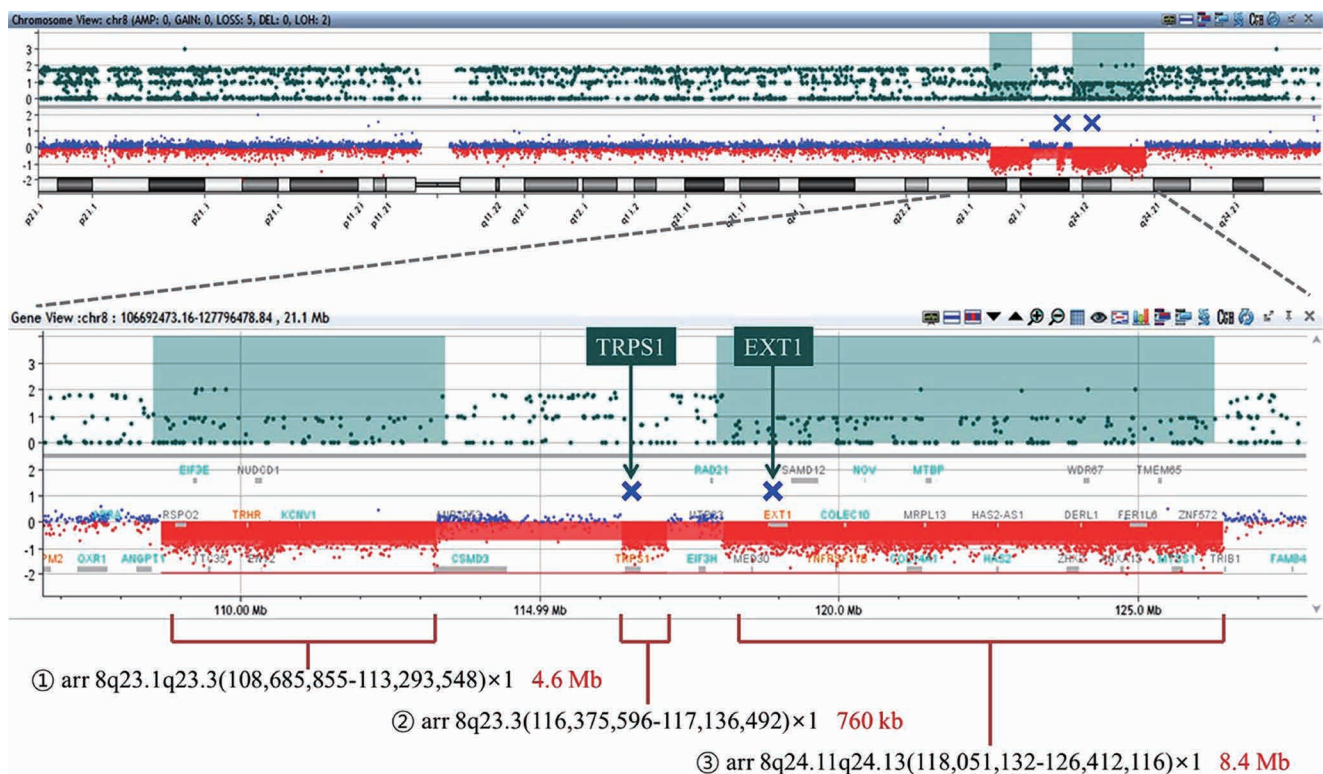


Fig. 2. Array CGH analysis of the genome of the patient shows three interstitial deletions from 8q23.1 to 8q24.13, arr[GRCh37] 8q23.1q23.3(108685855_113293548)x1, arr[GRCh37] 8q23.3(116375596_117136492)x1, and arr[GRCh37] 8q24.11q24.13(118051132_126412116)x1.

Table 1. Clinical features of this case compared to those of Langer-Giedion and Cornelia de Lange syndromes, and that presented by other patients with complex chromosomal rearrangements

Clinical characteristics	Our patient	Cappuccio et al. [3]	LGS	CdLS
Short stature	+	+	+	+
Microcephaly	-	+	+	+
Brachycephaly	+	+	-	-
Thick, arched eyebrow	-	+	-	+
Synophrys	-	-	-	+
Bulbous nose	+	-	+	-
Thickened alae nasi	+	-	+	-
Long philtrum	-	+	-	+
Prominent philtrum	-	-	+	-
Thin upper lip	-	+	-	+
Large prominent ears	+	+	+	-
Sparse scalp hair	+	-	+	-
Hirsutism	-	+	-	+
Cone-shaped epiphyses	-	-	+	-
Exostoses	-	+	+	-
Clinodactyly	+	+	+	+
Brachydactyly	-	-	-	+
Congenital heart defect	-	+	-	+
Cognitive impairment	+	+	+	+

Abbreviations: LGS, Langer-Giedion syndrome; CdLS, Cornelia de Lange syndrome.

TRPS1 is a zinc finger transcriptional repressor involved in the regulation of chondrocyte and perichondrium development. Trichorhinophalangeal syndrome type I (TRPS1) and type III (TRPS3) are caused by a heterozygous mutation in *TRPS1* [6]. TRPS1 patients have facial anomalies such as sparse scalp hair, a nose with a bulbous tip, a long flat philtrum, thin upper vermilion border, and protruding ears, skeletal abnormalities such as cone-shaped epiphyses at the phalanges and hip malformations, and short stature. *EXT1* has a role in regulation of chondrocyte differentiation, ossification, and apoptosis, and is a causative gene in multiple exostoses type I that is characterized by multiple projections of bone capped by cartilage in the metaphyses of long bones and the diaphyses of long bones [7]. TRPS2, also known as LGS, is caused by the loss of functional copies of *TRPS1* and *EXT1*, and has combined features of TRPS1 and multiple exostoses. Our case mainly presented with the phenotype of TRPS1 because the onset of multiple exostoses occurs from early childhood (2–3 years) to puberty [8].

TRHR is related to isolated central hypothyroidism. In our case, the thyroid function was within the normal range (T3 [156 ng/dL], free T4 [1.3 ng/dL], and TSH [1.9 μ U/mL]). Mutations in *TNFRSF11B*

cause juvenile onset Paget disease, which is autosomal recessive disorder. Mutations in *COLEC10* cause an autosomal recessive disorder called 3MC syndrome 3. Mutations in *TAF2* cause autosomal recessive mental retardation. *RNF139* is related to renal cell carcinoma in translocation t(3;8)(p14.2;q24.1). Homozygous mutations in *NDUFB9* cause mitochondrial complex I deficiency. Mutation in *WASHC5* cause spastic paraplegia 8, an autosomal dominant disorder, and Ritscher-Schinzel syndrome 1, an autosomal recessive disorder. Mutation in *NSMCE2* causes an autosomal recessive disorder called Seckel syndrome 10. Our patient did not show specific phenotypes associated with mutations in these genes, presumably because most of these gene mutations function in an autosomal recessive manner and *WASHC5* mutation with its autosomal dominant mode, causes adult onset spastic paraplegia.

Nearly 70% of LGS patients exhibit mild to moderate cognitive disability [3, 9, 10]. Although developmental delays and disabilities in LGS have been attributed to the deletion of genes outside the *TRPS1–EXT1* interval, the identity of the specific genes involved, is still under investigation. The size of the 8q deletion is directly correlated with intellectual disability [3, 11]. The developmental delay in our patient was moderate, which was probably related to the large deletion in 8q. In LGS, some patients have short stature due to deficiencies of the growth hormone [11]. Our patient showed delayed growth in weight and height during follow-up examinations.

This was a sporadic case of LGS with three-way translocation. This diagnosis was based on clinical findings and was confirmed by cytogenetic analysis, MLPA, and array CGH, which showed deletions of *TRPS1* and *EXT1* that are localized to the 8q23.3–8q24.11 region. To the best of our knowledge, this is the first report of LGS with complex translocation in Korea.

요 약

Langer-Giedion 증후군은 매우 드문 유전질환으로, *TRPS1*과 *EXT1* 유전자를 포함하는 8q24.1 위치의 결실에 의해 발생하는 질환이다. 생후 5개월 된 여아가 양측 엄지의 측만지증과 약화로 내원하였다. 환자의 핵형은 46,XX,der(4)t(4;19)(q27;q11),der(8)t(4;8)(q27;q22.3),der(19)t(8;19)(q22.3;q11)del(8)(q23q24.1)이었으며, multiplex ligation-dependent probe amplification (MLPA) 분석에서 rsa 8q24(P064)x1 및 rsa 8q24(P245)x1의 이형접합 결실을 보였다. Array comparative genomic hybridization (CGH) 분석 결과 8q23.1–q24.13에서 총 13.7 Mb에 걸친 3개의 중간 결실이 관찰되었다. 환

아의 임상적 증상과 염색체분석, MLPA 및 array CGH의 결과에 따라 환아는 3방향복합전위를 동반한 산발성 Langer-Giedion 증후군으로 진단되었다. 본 증례는 Langer-Giedion 증후군에서 복잡한 염색체 재배열을 보이는 국내 첫 보고이다.

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